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Association between idiopathic pulmonary fibrosis and lung cancer

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ABSTRACT

The morbidity of lung cancer in patients with idiopathic pulmonary fibrosis (IPF) ranges from 3% to 22%, significantly shortening the lifespan. However, the mechanisms by which IPF increases morbidity and mortality in lung cancer are not well understood. Lung cancer with IPF is more frequently observed in the peripheral regions of the lungs and in honeycomb areas. Squamous cell carcinoma is the most common cell type in lung fibrosis. Mechanisms such as proliferation, metastasis, angiogenesis, cancer stem cells, immunology, epigenetics, and metabolism may contribute to the initiation and progression of lung cancer in IPF patients. 2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) combined with computed tomography (CT) can assist in reliably detecting cancer. Surgery, chemotherapy, and radiation may trigger exacerbations of fibrosis. The increased use of wedge resection, proton therapy, and immunotherapy may reduce the risk of exacerbations, thereby improving survival.

Keywords: Interstitial lung disease, idiopathic pulmonary fibrosis, lung cancer

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is an interstitial lung disease with an unknown etiology, poor clinical prognosis, and progressive, irreversible nature. Patients with IPF are at a higher risk of developing lung cancer compared to healthy individuals. The reported incidence of lung cancer in these patients is between 11.2 and 36 cases per 1.000 persons annually.[1] Patients with IPF, the cumulative incidence of lung cancer significantly increases, varying from 1.1% in one year, 8.7% in three years, 15.9% in five years, and reaching 31.1% in a decade of follow-up. Factors increasing the risk of lung cancer include advanced age, male sex, decreased lung function [more than a 10% decline in force vital capacity (FVC), low carbon monoxide diffusion capacity (DLCO)], and smoking.[2] The prevalence of lung cancer is 9 times higher in patients with combined pulmonary fibrosis and emphysema (CPFE). Additionally, higher rates of lung cancer are observed in IPF lung transplant recipients, suggesting shared molecular links between these two diseases.[3] The most common histological type of lung cancer in individuals with IPF is squamous cell carcinoma, followed by adenocarcinoma, which is more frequently seen in the lower lobes. Furthermore, mucinous adenocarcinoma is reported to be more common in IPF patients.[4] The 5-year survival rate for lung cancer patients with IPF is 14.5%, while it is 30.1% in those without IPF.[5]

PATHOPHYSIOLOGY

The shared molecular pathways between established lung cancer and pulmonary fibrosis include epithelial-mesenchymal transition (EMT), mesenchymal activation, and mutations in pulmonary-surfactant associated proteins (SFTP).[6] Histopathological features of IPF include fibroblast foci, subpleural fibrosis, and honeycomb structures.[7] Most lung cancer cases associated with IPF are located in areas related to IPF and have a worse prognosis.[8] The mechanical forces generated in IPF promote the initiation and progression of lung cancer. Mechanical stimulation not only directly activates the proliferation signaling pathways of local cancer cells and promotes their spread by providing a dense growth factor microenvironment, but it also supports cancer progression by awakening dormant cancer cells.[9] Mechanical disruption globally regulates the epigenetic response (chromatin accessibility, DNA methylation, and non-coding RNA), facilitating cancer progression. Mechanical forces originating from IPF lung tissue sustain angiogenesis by promoting the proliferation, differentiation, and migration of endothelial cells. Specific gene mutations, including microsatellite instability, fragile histidine triad, oncoprotein p53, and loss of heterozygosity, have been observed in many IPF cases, especially in the characteristic peripheral lung regions with honeycomb appearance.[10] Mutations affecting telomere shortening and telomerase expression are also found in familial IPF cases. Janus kinase and SFTP mutations have been found in families with both IPF and lung cancer association.[11]

The mechanical cues arising from the fibrotic response in IPF help cancer cells maintain stem cell properties. The

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mechanical environment in IPF modulates the immune microenvironment by promoting the infiltration of pro-tumorigenic macrophages, programmed death ligand 1 (PD-L1) expression, the transition from M0 to M2 macrophages, and the release of transforming growth factor-β1 (TGF-β1) from mast cells. The mechanical forces in IPF can prime premalignant cells for proliferation by activating glycolysis and providing energy to sustain proliferation and metastasis.[12] Transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) play roles in both lung cancer and pulmonary fibrosis, with VEGF potentially promoting cell survival and proliferation through extracellular signal-regulated kinase 1/2 (ERK1/2) and phosphoinositide 3-kinase (PI3K) activation. VEGF messenger ribonucleic acid (mRNA) is elevated in endothelial progenitor cells from IPF patients.[13] TGF-β receptors lead to changes in cellular behavior, and low receptor levels promote metastasis and cancer progression, playing a crucial role in early carcinogenesis. Chronic inflammation is a common feature in both pulmonary fibrosis and tumor development.[14] The inflammatory microenvironment in the lungs includes the initiation and progression of cancer cells, excessive collagen accumulation, and other ECM components, leading to tissue remodeling. This altered lung architecture and increased stiffness can create a microenvironment supportive of cancer cell growth which may involve changes in the ECM and cytokine profiles.[6] Both in cancer and pulmonary fibrosis (particularly IPF), molecules like fascin, laminin, and heat shock protein 27, which are associated with cell migration and invasion, are expressed in bronchiolar basal cells and epithelial cells around fibroblast foci, contributing to the invasive front of tumors.[15] Furthermore, matrix metalloproteinases and integrins, known for their roles in cell invasion, are strongly linked to the development of stem cell-like properties in cancer cells and, in the context of IPF, promote the initiation, maintenance, and resolution of tissue fibrosis. Clinical trials are investigating inhibitors such as the humanized antibody STX-100 and specific antibodies against αvβ6.[16] Epithelial-to-mesenchymal transition (EMT) is a process where epithelial cells undergo changes to become more mesenchymal, and the transition of cells from an epithelial to mesenchymal phenotype can promote tissue remodeling. EMT can contribute to tissue remodeling in the lungs and create a microenvironment that supports cancer growth.[17] Circulating and cell-free deoxyribo nucleic acid (DNA) and abnormal mRNA levels are considered diagnostic and prognostic biomarkers for both cancer and IPF. The abnormal expression of specific non-coding RNAs in IPF affects genes related to fibrosis, extracellular matrix (ECM) remodeling, EMT induction, and apoptosis, potentially contributing to functional impairment in patients with lung fibrosis.[18]

DIAGNOSIS

It is important to carefully compare CT scans to identify new solitary nodules. Due to the increased risk of lung cancer in IPF, high-resolution computed tomography (HRCT) should definitely be considered in these patients. New pulmonary nodules should be evaluated further according to the high-risk group criteria of the Fleischner guidelines.[1] Additionally, mediastinal lymph node enlargement is common in interstitial lung disease (ILD) patients, which reduces the specificity of this method for detecting lung cancer.[19] For nodules larger than 8 mm, positron emission tomography and computed tomography (PET CT) should be requested. Suspicious mediastinal lymph nodes can be sampled using endobronchial ultrasound-guided transbronchial needle biopsy (EBUS-TBNB) and radial EBUS for peripheral lesions.[20] Biopsy under CT guidance should be planned for patients with neoplastic lesions suspected, and it should be remembered that the risk of complications such as pneumothorax due to the procedure may be higher. A "liquid biopsy" aimed at revealing driver mutations and determining individualized treatment for frail patients could also be considered.[11]

TREATMENT

The treatment of lung cancer in patients with fibrosis is complex: surgery, chemotherapy, and radiation can trigger exacerbations of fibrosis and increase the likelihood of poor outcomes.[21] Since patients with ILD often have impaired lung function, advanced age, and numerous comorbidities, surgical procedures pose a risk factor for increased morbidity and mortality.[22] In a study of patients with cancer stage IA, 5-year postoperative survival rates in IPF patients were reported as 61.6%, compared to 83.0% in those without IPF.[23] The extent of surgical resection is also associated with mortality.[24] Larger procedures lead to more complications, including acute exacerbations, acute lung injury/acute respiratory distress syndrome, and higher postoperative mortality. In patients where lobectomy is not recommended, segmentectomy and wedge resection show comparable survival rates.[25] Compared to wedge resection, performing lobectomy or segmentectomy had an odds ratio (OR) of 3.83, and performing pneumonectomy or lobectomy had an OR of 5.7 for acute exacerbation of interstitial lung disease (AE-ILD).[26] As less lung is compromised in wedge resection, better outcomes are predicted, as seen with wedge resection.[27]

Radiation therapy for lesions in the lungs is generally indicated for early-stage non-small cell lung cancer (NSCLC) patients who are not candidates for surgery due to poor lung function or comorbidities, R1 surgical resection cases, and locally advanced NSCLC patients combined with chemotherapy.[28] Stereotactic body radiation therapy (SBRT) is an effective, non-invasive method for early-stage NSCLC patients who are not suitable for surgical resection. A well-known side effect of radiation therapy is radiation pneumonia.[29] Pulmonary toxicity occurs in 1.5-20% of patients receiving SBRT and in 5.0-25% of patients receiving standard fractionated radiation therapy. Proton beam therapy (PBT) is a newer treatment for NSCLC patients with early-stage disease and centrally located lesions, with the major advantage of delivering less scattered radiation.[30] However, PBT is not widely available, and more research is needed to demonstrate its hypothetical effectiveness for treating lung cancer. Due to potential harmful effects, radiation therapy is not commonly used in IPF patients. According to a recent retrospective, multicenter European study, only a small percentage (12.5%) of patients diagnosed with both IPF and lung cancer received radiation therapy.[31] However, radiation therapy, especially SBRT, should be considered for carefully selected patients with both IPF and lung cancer.[32]

Percutaneous image-guided ablation, sub-lobar resection, and SBRT are techniques used to treat small tumors in early-stage NSCLC with outcomes such as radiofrequency, microwave, or cryoablation. Complications such as pneumothorax, bronchopleural fistula, and pneumonia have been reported. Due to its localized effects, this approach may be valuable in ILD patients, although data are limited.[11]

Chemotherapy plays a significant role in the treatment of locally advanced and metastatic lung cancer patients.[33] A recent meta-analysis showed that acute exacerbations following chemotherapy are more common in patients with IPF compared to those without.[34] In patients with IPF and small cell lung cancer (SCLC), acute exacerbation after first-line treatment is significantly higher in IPF patients compared to those with NSCLC (31% vs. 63%).[35] Some medications increase the risk of pneumotoxicity and AE-ILD. In patients with advanced-stage NSCLC-IPF, the combination of carboplatin and etoposide showed similar mortality benefits in stage III NSCLC-IPF patients and those without IPF.[36] Another study examining the effects of carboplatin and etoposide (or paclitaxel) in fibrotic lung cancer patients reported similar median progression-free survival but poorer overall survival in fibrotic lung cancer patients.[37] Among 684 ILD patients who received first-line chemotherapy for SCLC, the acute exacerbation rate in the context of chemotherapy was approximately 8%, with lower rates observed in nab-paclitaxel-containing regimens (5%) compared to other regimens (12%).[38] The reported ILD exacerbation rates for patients receiving docetaxel or gemcitabine were 28% and 43%, respectively, while vinorelbine was not associated with AE-ILD in a small retrospective study. Pemetrexed has shown increased toxicity in IPF patients compared to other ILD patients and significantly higher toxicity compared to patients without underlying ILD.[39]

New clinical trials are testing the efficacy of specific monoclonal antibodies and tyrosine kinase inhibitors. Targeted therapies such as epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) or anaplastic lymphoma kinase inhibitors (ALK) have been associated with pneumotoxicity.[40] A recent meta-analysis reported male gender, smoking history, and pre-existing ILDs as risk factors for EGFR-TKI-induced ILDs. Pre-existing ILD has been associated with a sixfold increased risk of developing EGFR-TKI-induced ILD.[41,42] Further studies are needed on the use of other inhibitors for ALK, EGFR, c-ros oncogen1 (ROS1), and v-Raf murine sarcoma viral oncogene homolog B (B-RAF) in patients with pulmonary fibrosis and lung cancer.[27] A study found no acute exacerbation of pulmonary fibrosis in any patients when pirfenidone was added to immune checkpoint inhibitors or carboplatin-based chemotherapy for the treatment of NSCLC. Furthermore, nintedanib, a tyrosine kinase inhibitor, has been successfully used in combination with docetaxel for advanced-stage NSCLC treatment.[43] The anti-VEGF antibody bevacizumab has been tested in patients with ILD and lung cancer, and it was reported to prevent chemotherapy-induced AE-ILD.[44] A recent meta-analysis examining the effect of anti-VEGF treatments like nintedanib, bevacizumab, and ramucirumab on EGFR-TKI-induced ILD found that combining EGFR-TKIs with anti-VEGF agents was associated with a significant reduction in ILD incidence compared to EGFR-TKI monotherapy. Nintedanib's combination with EGFR-TKIs may have significant effects such as reducing pneumotoxicity and slowing tumor growth.[45]

PD-1 mediates the up-regulation of Interleukin-17 (IL-17) and TGF-β production by PD-1+Thelper (Th) 17 cells through signal transducer and activator of transcription 3 (STAT3), which promotes lung fibrosis, and PD-1 inhibits the diferentiation of cluster of differentiation 4 (CD4)+T cells to T regulator (Treg) cells, which promotes the production of type I collagen and inhibits myofbroblast proliferation; PD-L1 on lung fbroblasts inhibits myofbroblast proliferation by inhibiting the p53 pathway and activating the focal adhesion kinase (FAK) pathway, causing myofbroblasts to evade phagocytosis, leading to excessive proliferation of myofbroblasts, resulting in lung fbrosis. In addition, PD-L1 mediates lung fbroblast-to-myofbroblast transformation (FMT) through Smad3 and β-catenin signaling pathways, thus promoting lung fbrosis; PD-L1 upregulation on lung fbroblasts promotes fbrosis by inhibiting autophagy leading to myofbroblast proliferation and ECM deposition.[46] Immunotherapy refers to immune checkpoint inhibitors (ICIs) and includes programmed death-1(PD-1) inhibitors such as nivolumab and pembrolizumab and PD-L1 inhibitors such as atezolizumab and durvalumab. In patients with ILD and lung cancer, PD-L1 levels are similar to those without ILD, and increased tissue levels of PD-L1 are associated with better outcomes.[47] Mediastinal lymph nodes of mice treated with bleomycin showed increased size and higher PD-1 and PD-L1 mRNA levels compared to controls, while pembrolizumab weakened bleomycin-induced fibrosis. The use of combination regimens or monotherapy with immunotherapy has not been widely tested in lung cancer patients with IPF. A meta-analysis including 10 studies of NSCLC treated with ICIs showed that patients with pre-existing ILD had significantly higher (almost twice as high) overall response rates compared to those without ILD. In patients with pre-existing ILD disease control rates and progression-free survival were similar to those without ILD.[48] ICIs, while enhancing the normal immune response, may enhance the anti-tumor efects of cellular immunity, leading to an immune tolerance imbalance and immunerelated adverse events (irAEs). Studies have found that the use of ICIs in patients with ILD is associated with a higher risk of developing immune checkpoint inhibitors related pneumonitis (CIP) than that in patients without ILD.[49] Currently, no studies have directly validated the utility of PD-1/PD-L1 inhibitors on pulmonary fbrosis, and conclusive experimental evidence to support their therapeutic value is scarce. Studies have shown that ICIs in patients with IPF combined with squamous cell carcinoma, the addition of antifibrotics may prevent drug-induced pneumonia or acute exacerbation of IPF. Therefore, the study of the potential mechanism of irAEs not only contributes to the immunotherapy of tumors but also plays an important role in the treatment of IPF. Whether the combination of ICIs and antifbrotic drugs can delay the pathogenesis of IPF can be considered as a research direction.[50,51]

CONCLUSION

The presence of pulmonary fibrosis in individuals with lung cancer affects both the treatment approach and prognosis. Due to impaired lung function, treatment options may be

limited, and prognosis may be worse compared to lung cancer alone. Early diagnosis of lung cancer and more effective treatment could benefit from PET-CT screening. Sub-lobar surgical resections, immunotherapy, and proton therapy show potential. Further research is needed regarding the survival and quality of life of these patients.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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